5. Global Issues

Modern transportation has allowed for the rapid transmission of infectious diseases across the globe. SARS rode halfway around the world on an airplane to reach Canada. This example illustrates the necessity for solidarity amongst the nations to protect themselves and each other against such threats to global health. In light of the interconnected nature of today's world, it is neither ethical nor acceptable to conceal health information that can protect others. Had China stepped forward earlier with information about the disease and its origins, the spread of SARS may have been reduced. To establish effective global health protection, Dr. Peter Singer and colleagues encourage transparency, honesty, and good communication within the worldwide community.

Conclusion

Sudden outbreaks of diseases like SARS place enormous stress on the health care system and force health care providers to make difficult ethical decisions that require the prioritization of various values. Careful consideration of the benefits and costs to patients, the public, health care providers, and other nations must be taken into account. Decisions should simultaneously respect individual liberty, personal privacy, proportionality, and reciprocity while upholding health care workers' duty to caring and protecting the public from harm. M

For the full version of the article, read:
Ethics and SARS: lessons from Toronto (Singer et al., 2003)

Preparing for the Next SARS Epidemic

Exploring Treatment Development and Vaccination Options

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On October 16, 2002 the first case of Severe Acute Respiratory Syndrome (SARS) was reported in Guangdong Province of the People's Republic of China (Hawkey, Bhagani & Gillespie, 2003; Stavrinides & Guttman, 2003). The outbreak of SARS then spread from Guangdong to more than 30 countries around the world, using air travel as a means of dissemination (Stavrinides & Guttman, 2003). As illustrated by the World Health Organization (WHO) in a report entitled "Severe acute respiratory syndrome (SARS): status of the outbreak and lessons for the immediate future", there are several aspects of SARS that make it particularly dangerous. The first and perhaps most imperative feature is that there is currently no vaccine or treatment for this new virus. The lack of medicinal tools forced doctors to resort to quarantine in attempt to halt the spread of SARS. Even diagnosis of the disease was difficult, as the initial symptoms of SARS are common to other viruses, like influenza, and may vary amongst patients. Detection of the virus is further complicated by the testing limitations. These tests may result in improper diagnosis if inaccurately conducted or incorrectly analyzed. With these complications aside, the initial stages of SARS seemed to affect the health care system more than the general public (Emanuel, 2003). Over half of the initial 60 reported cases of SARS were health care workers. Once the epidemic spread to Canada, SARS continued to subject the lives of our health care professionals at risk. From February 23, 2002 to May 14, 2003, 65% of suspected Canadian SARS cases were health care workers (Emanuel, 2003).

In the struggle to contain the growing epidemic, the WHO issued a global alert on March 12, 2003 (Groneberg, Zhang, Welte, Zabel & Chung, 2003). This warning, along with the quarantine of infected individuals, face masks, and preventative measures, were implemented in hospitals and on the general public, and allowed SARS to be contained before it became uncontrollable. Although the 8098 cases of SARS and 774 resultant deaths (reported by the WHO as of July 11, 2003) may appear minute compared to the millions of deaths resulting from other viral

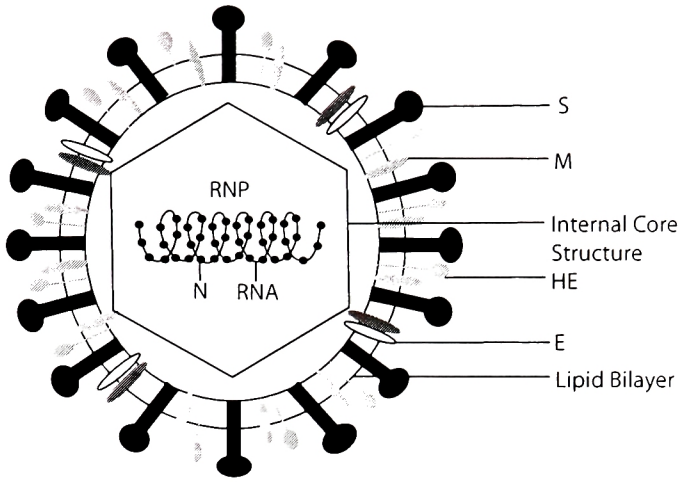

FIGURE 1
A model of typical coronavirus structure: S, spike glycoprotein; M, membrane glycoprotein; E, small envelope protein; HE, hemagglutinin-esterase glycoprotein; N, nucleocapsid phosphoprotein; ICS, internal core-shell composed of M glycoprotein; NC, nucleocapsid.

infections, the novelty and high mortality rate of SARS caught the attention of the world and challenged the world's public health systems to respond quickly to new health threats (Emanuel, 2003). While it may appear that SARS has been contained, possibilities of a second outbreak have already been explored. As Guan Yi, a microbiologist from the University of Hong Kong, pointed out to *Science,* "The animals are the same, human activity is the same, the farms are the same, and the virus is still around. There is no reason to doubt the virus will be back" (cited from Enserink & Normile, 2003). These fears have recently been fulfilled when a Taiwanese researcher accidentally contracted SARS while working in a high security laboratory. To make matters worse, the scientist might also have infected his colleagues during a conference before any symptoms had manifested. This stands as an important reminder that SARS still has the potential to create another epidemic, and thus it is imperative that we develop effective methods to prevent or treat this virus.

CAUSES AND ORIGINS OF SARS

A large number of studies have concluded that SARS is caused by a novel coronavirus, termed SARS-CoV (Chen, Ou, Zhang & Zhang, 2003). All viruses in the coronaviridae family are positive stranded viruses named for their appearance under an electron microscope. The glycoprotein spikes covering the outer membrane of the virus resemble a corona, or halo, when stained and viewed under extremely high magnification (Fig. 1) (Lai et al., 2001). These glycoprotein spikes act as specialized viral fusion proteins, allowing the virus to overcome the phospholipid bilayer by binding to specific receptor molecules on the surface of the host cell (Bosch, van der Zee, de Haan & Rottier, 2003). Once the virus and the host cell have fused, the virus will use the host cells' metabolic machinery to replicate its own genome and produce the proteins necessary for the creation of additional viruses (Fig. 2) (Campbell & Reece, 2002).

When the genomic sequence of SARS was completed, it was noted that the SARS-CoV was distinct from other coronaviridae family members (Zeng et al., 2003). This difference was observed by studying the regions of the viral genome that code for proteins, termed open reading frames (ORFs). The ORF that codes for the surface glycoprotein spikes, along with a membrane protein and a nucleocapsid protein, have nucleotide sequences that are unlike those of any other coronavirus. It is for this reason that some researchers believe SARS-CoV should be classified as its own distinct group (IV) of the coronaviridae family. As well, a large ORF that codes for SARS viral enzymes is unique to SARS, sharing less than 50% similarity to other coronaviridae viruses. The results of this 2003 study, conducted by Zeng et al., also found three unknown ORFs that are not found in any other coronavirus. This confirms that SARS is unlike any other virus we have dealt with in the past.

Despite the establishment of the unique SARS-CoV genome, questions concerning the evolutionary pathway of this virus are still left unanswered. Attempts

are being made to locate the particular species from which SARS first evolved and spread to infect the citizens of Guangdong. It has been recently reported by Enserink that the SARS virus can be isolated from masked palm civets (a cat-like animal) found in food markets (2003). However, this does not irrefutably prove that SARS originated from civets, only that these animals are carriers of the virus. Civets may have been infected with the virus by another organism (Enserink & Normile, 2003). With these findings, attempts are being made to conclusively determine the species of origin.

While the hunt for the vector continues, research is being conducted to determine the viral species that evolved into the SARS virus. Studies of the SARS-CoV genome by Stavrinides and Guttman compared the SARS ORFs with those of other viruses to find similarities in their genetic codes (2003). What they found was that the SARS virus may actually be a combination of mammalian and avian viruses. The membrane and nucleocapsid proteins produced by the SARS-CoV are similar to those produced by a coronavirus that infects birds, the avian infectious bronchitis coronavirus; however, analysis of another SARS protein, the replicative polyprotein (PP1ab), ascertains that it is more similar to members of the coronaviridae family that infect humans. The theory that SARS evolved from both avian and mammalian viruses is further strengthened when the ORF that codes for the surface glycoprotein spikes (S) is analyzed. The SARS S protein shares commonalities to the S proteins of both the mammalian and avian viruses mentioned above, suggesting that genetic recombination may have occurred between these members of the coronaviridae family (Stavrinides & Guttman, 2003). While this research provides insight into the ancestry of the SARS-CoV, the specific species responsible for transmitting SARS into the human population is still ambiguous. Until there is a greater understanding of this virus, SARS will continue to be a threat for epidemics.

Development of SARS Vaccines and Anti-Viral Drugs

Important research is being conducted at McMaster University concerning the development of vaccines for the SARS-CoV. As described in a 2003 McMaster article entitled "McMaster researchers race to SARS vaccine development", professor Jim Mahony's work has aided greatly in the development of potential vaccines. Mahony cloned an important SARS-CoV nuclear protein (SARS-N), which was then inserted into an engineered form of an adenovirus (cold virus) by a research team lead by Jack Gauldie. This team, which is composed of McMaster researchers, includes Frank Graham, Mary Hitt, Ludvik Prevec, Uma Sankar, and Mahony. As mentioned in the article, a second engineered cold virus was constructed to contain the Spike SARS gene (SARS-S), obtained through collaboration with the SARS Vaccine Initiative of the British Columbia Centre for Disease Control. When these modified adenovirus vectors were injected as vaccines, a strong antibody response was induced, particularly against the SARS-S protein, and provided immunity to the virus (Fig. 3). This reaction could prevent the individual from becoming infected with SARS-CoV, since antibodies to the Spike protein would neutralize the virus. The article also asserts that, should the virus evade the neutralization stage of protection, expression of the nucleoprotein (SARS-N) by the recombinant adenovirus vaccine would stimulate a potent lymphocyte-mediated protection that would help destroy cells infected with SARS-CoV. Animal testing is currently being conducted to determine whether the vaccine is safe for human trials, but this research demonstrates that the development of a SARS vaccine is promising.

Additional investigations are being conducted in search of medications that could aid those who become infected with SARS. The objective of such antiviral drugs is to disrupt viral functions by rendering important proteins or enzymes useless. However, specific antiviral medication, based upon the 3-dimensional structures of the SARS-CoV proteins cannot yet be produced (Spiga et al., 2003). Since the genome of SARS is so unique, it is not enough to simply compare the protein products of the SARS-CoV to other members of the coronaviridae family. The homology of the SARS spike glycoprotein to other viruses in its family range from 20.39% to 27.63%. This low percentage suggests that these proteins have very different structures. Current antiviral drugs

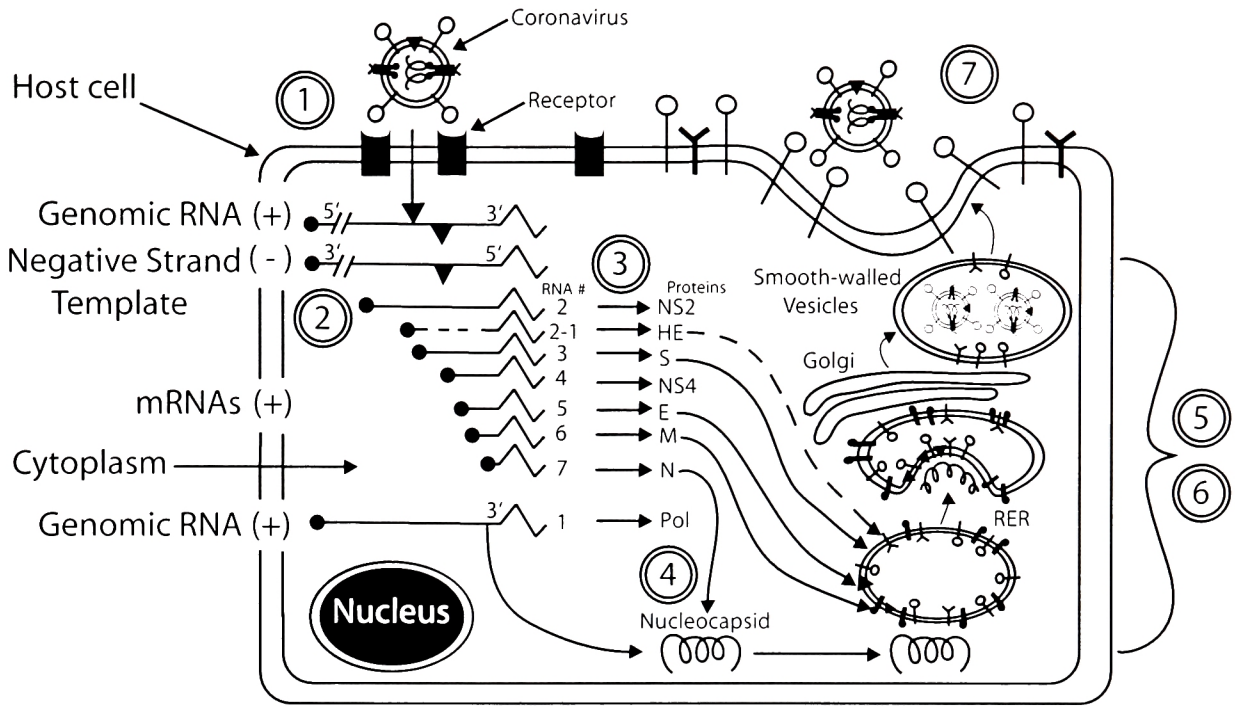

FIGURE 2

The coronavirus replication cycle: (1) Virions bind to the plasma membrane by interaction of the spikes with specific receptor glycoproteins or glycans. Penetration occurs by S protein-mediated fusion of the viral envelope with the plasma membrane or endosomal membranes. (2) The gene 1 of viral genomic RNA is translated and processed to yield an RNA-dependent RNA polymerase (Pol) and other proteins involved in viral RNA synthesis. The Pol products use the genomic RNA as a template to synthesize negative-stranded RNAs, which are, in turn, used to synthesize genomic RNA and subgenomic mRNAs. (3) With a few exceptions, each mRNA is translated to yield the structural proteins N, M, E, S, and HE and several non-structural proteins. (4) The N protein and newly synthesized genomic RNA assemble in the cytoplasm to form helical nucleocapsids, which bind to the M protein at the budding compartment that lies between the RER and the Golgi. (5) Similarly, E protein is also transported through the ER to the Golgi, where E and M proteins interact to trigger the budding of virions, enclosing the nucleocapsid. (6) The S and HE glycoproteins are also translated on membrane-bound polysomes, inserted in the RER, and transported to the Golgi complex. (7) Virions are apparently released by exocytosis-like fusion of smooth-walled, virion-containing vesicles with the plasma membrane. Virions may remain adsorbed to the plasma membranes of infected cells (Lai, M.M.C. et al., 2001).

designed to disrupt the spike glycoprotein of one coronavirus would therefore most likely not hinder the cell recognition of a SARS virus (Spiga et al., 2003). Development of SARS antiviral medication that targets the S protein can only commence once there is a greater understanding of its structure.

Along with the S protein, the main cysteine proteinase (Mpro) of the SARS virus is seen as a likely target for antiviral drugs (Yan et al., 2003). Recent models developed for the structure of this enzyme, which is important for the processing of polypeptides, suggests there is a fold that can also be found in the human rhinoviral protease (3Cpro) (Anand et al., 2003; Yan et al., 2003). Although the SARS Mpro and rhinoviral 3Cpro enzymes have very different nucleotide sequences, the common fold places their ligand-binding sites in the same position (Yan et al., 2003). This similarity in active site implies that drugs developed to treat the common cold may be effective against SARS (Anand et al., 2003; Yan et al., 2003). However, other research using these models have suggested that drugs developed to treat HIV may be a better starting place for the development of SARS Mpro inhibitors. Based on current models, it was found that HIV-1 protease inhibitors would have a greater affinity for SARS Mpro active sites compared to human anti-rhinoviral medication (Jenwitheesuk & Samudrala, 2003). Such comparisons allow

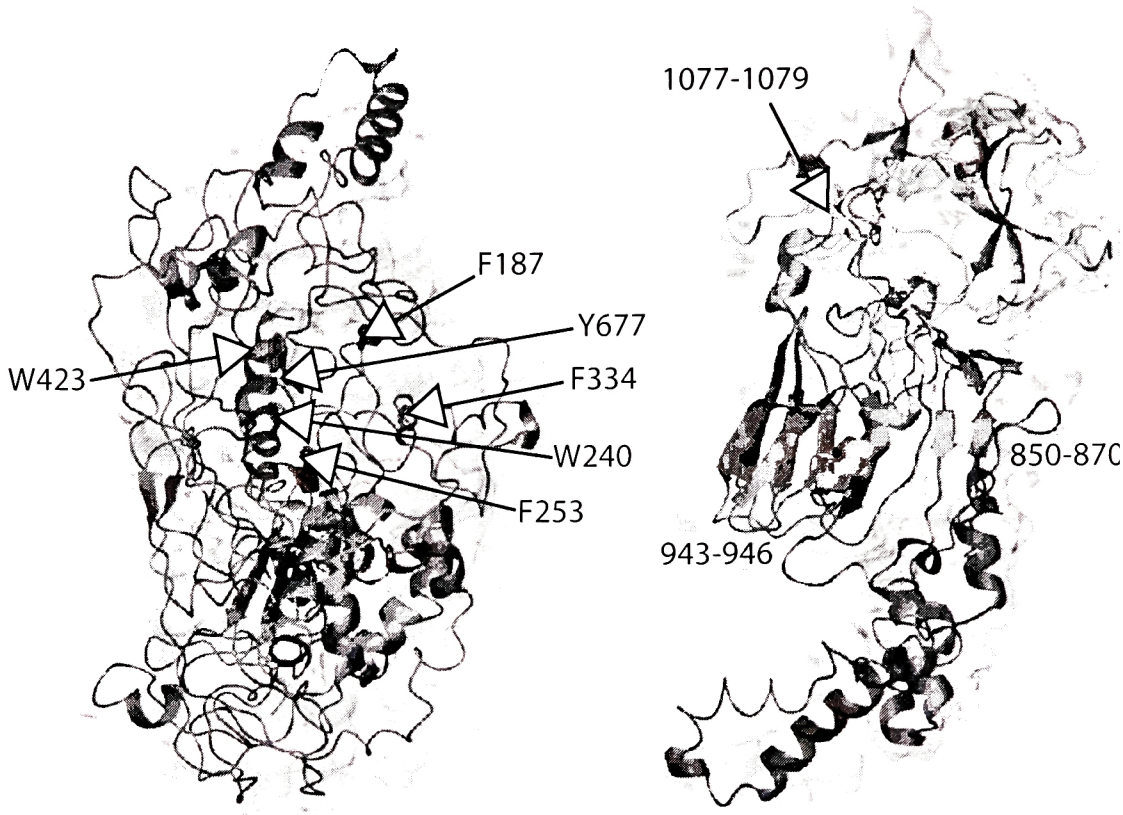

FIGURE 3
Surface and ribbon representations of the tertiary structure of the S1 and S2 subunits of SARS-CoV S glycoprotein that may be used as targets for vaccines.

researchers to determine the most logical starting point to develop an anti-SARS medication, but the potential for existing drugs to act on SARS proteins is not limited to the Mpro enzyme. Other enzymes that are crucial for the survival of this coronavirus are also being examined as prospective targets for anti-SARS drugs. The SARS-CoV RNA polymerase, an enzyme that links RNA nucleotides together, displays slight homology to the polymerase of the hepatitis C virus (Campbell & Reece, 2002; Yan et al., 2003). This may imply that drugs that inhibit the HCV polymerase may also inhibit, to some degree, the SARS RNA polymerase. Despite such ground-breaking research, there is currently no drug available for use against SARS. Hopefully, research advances in the near future would lead to the development of an anti-SARS medication.

Although the SARS outbreak was a stressful, often dangerous, period of time for the health care profession, important lessons were learned. The WHO pointed out in a May 2003 outbreak report that the quick containment of SARS demonstrated the ability of global alerts to educate the public and scientific community about new medical threats. However, initial cases of SARS may have gone unreported, which allowed the virus to quietly infect more individuals and generate a substantial outbreak. As well, this outbreak highlighted the necessity for certain health care changes to fight future epidemics. A disturbingly high percentage of SARS cases were health care workers, and hospitals were forced to impose admittance limitations, or close completely, because of the epidemic. Nonetheless, the scientific community was able to respond swiftly, and conducted research that could lead to the development of vaccines and anti-SARS drugs. Ultimately, this would enable our health care system to be better prepared if there is a re-emergence of severe acute respiratory syndrome. M